

## Education-Family Physician Corner

### When to Treat Influenza with Antiviral Drugs

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Influenza is a common highly contagious respiratory illness caused by RNA viruses (Orthomyxoviridae). It affects humans, other mammals and birds. Most common symptoms include chills, fever, sore throat, cough, body aches, headaches and generalized weakness. The severity of symptoms usually ranges between mild to severe and occasionally fatal. Elderly, children and patients with certain chronic diseases that compromise their immunity system are at risk of serious influenza complications such as pneumonia.

Seasonal epidemics are common worldwide; every year hundred thousands of influenza victims die of flu complications and adding huge economic burden on health services.

There are three major types of influenza viruses A, B and C. They are further divided into subtypes according to the strain determined by the surface protein. In the last century, three major influenza outbreaks were responsible for the deaths of millions<sup>1</sup>.

The influenza virus becomes more virulent when it evolves to a stronger strain through infecting animal species and then infecting humans. This process involves the introduction of new genes into the virus. One of the famous viruses is the swine flu virus which is nothing but an influenza type A virus namely H1N1. This virus had combined human, pig and bird genes and emerged as an outbreak in the US, Mexico and other countries. Despite the WHO declaration of the pandemic in 2009, the strain is less virulent than the common flu strains<sup>2,3</sup>.

### Symptoms and Signs

The symptoms are very similar to common cold except for the severity which tends to be more. They include, fever, sore throat, cough, headache, body aches, chills and nasal congestion. Call et al, presented the sensitivity and specificity of some of the most common symptoms and signs for the diagnosis of influenza, see table 1<sup>4</sup>.

**Table 1: Most Sensitive Symptoms for Diagnosing Influenza<sup>1</sup>**

Symptom	Sensitivity	Specificity
Fever	68-86%	25-73%
Cough	84-98%	7-29%
Nasal congestion	68-91%	19-41%

\*All three findings, especially fever, were less sensitive in patients over 60 years of age

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In early stages, it is difficult to distinguish between the common cold and Influenza patients, the latter tends to feel worse and often confined to bed for several days. They also tend to get moderate to high fever.

To prescribe antiviral drug, it is important to make the diagnosis at an earlier stage of the flu because it is effective if administered early. Therefore, the presence of all the symptoms listed in table 1 can markedly enhance the accuracy of the diagnosis<sup>5</sup>.

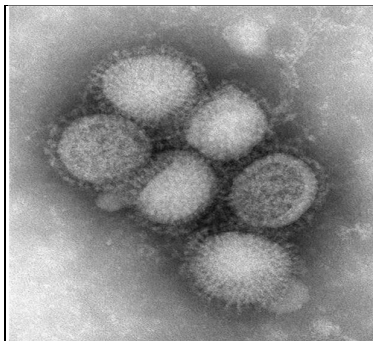
Occasionally, influenza can cause severe illness either because of secondary bacterial infection of the lung or as a result of the virus, a sign that the family physician should be alerted to especially if clinical improvement is followed by a sudden deterioration. The relapse is characterized by high fever and shortness of breath indicating the presence of pneumonia.

### **Types of Viruses**

There are three major types of RNA viruses that cause Influenza in humans; these are distinct from parainfluenza viruses that cause common upper respiratory tract infections:

1. Influenza virus A (most virulent)
2. Influenza virus B
3. Influenza virus C

Although there is one species of influenza A virus (figure 1), it is further subdivided to serotypes. On occasions the virus is transmitted to other mammals where it gets genetically altered and may cause devastating pandemics such as the ones which occurred during the last century.



**Figure 1: H1N1 Virus (CDC)**

Among the common serotypes of influenza A virus are<sup>6</sup>:

1. H1N1, caused Spanish Flu in 1918, and Swine Flu in 2009
2. H2N2, caused Asian Flu in 1957
3. H3N2, caused Hong Kong Flu in 1968
4. H5N1, caused Bird Flu in 2004
5. H7N7, has unusual zoonotic potential
6. H1N2, endemic in humans, pigs and birds
7. H9N2
8. H7N2
9. H7N3

## 10. H10N7

Influenza B virus is less common than influenza A virus, it infects humans exclusively. It tends to mutate less frequently than influenza A virus. Because it affects humans only, pandemics of this type do not occur<sup>7</sup>.

Influenza C affects humans, dogs and pigs; therefore, it tends to give rise to local outbreaks. However it is less severe especially in children<sup>6</sup>.

### Prevention

Hygienic measures play an effective role in limiting the spread of influenza viruses especially among health staff. Regular hand washing after contact with infected patients and the use of alcohol in combination with quaternary ammonium compounds or bleach markedly reduce the transmission<sup>8</sup>.

Closing schools, canceling social gatherings and theaters did not affect the overall death rate of influenza<sup>9</sup>.

Influenza vaccine is manufactured annually. It is particularly indicated for children, elderly, immunocompromised, diabetics, asthmatics and others, see table 2. However, the cost effectiveness of these vaccines is based on key assumptions<sup>10</sup>. There are several conditions in which the vaccine is contraindicated, see table 3.

**Table 2: Recommended Annual Flu Vaccine with Modifications<sup>11</sup>**

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- Elderly (aged 65 or above)
  - Patients with chronic lung diseases (asthma, COPD, etc.)
  - Patients with chronic heart diseases (congenital heart disease, chronic heart failure, ischemic heart disease)
  - Patients with chronic liver diseases (including cirrhosis)
  - Patients with chronic renal diseases (such as the nephrotic syndrome)
  - Patients who are immuno-suppressed (those with HIV or who are receiving drugs to suppress the immune system such as chemotherapy and long-term steroids) and their household contacts
  - People who live together in large numbers in an environment where influenza can spread rapidly, such as prisons, nursing homes, schools and dormitories
  - People who plan to attend or participate in a high profile important event (such as Hajj, Olympic Games, World Cup and the World's Fair)
  - People who are in the armed forces
  - Healthcare workers (both to prevent sickness and to prevent spread to patients)
  - Children from ages six months to two years
- 

**Table 3: Contraindications to the Seasonal Influenza Vaccine<sup>12</sup>**

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- Infants less than 6 months of age
  - An allergy to any component of the vaccine (such as MSG, arginine, gentamicin or gelatin)
  - Severe allergy to eggs
  - A known anaphylactic hypersensitivity to a previous dose of influenza vaccine or to any component of the vaccine (e.g., thimerosal)
  - History of Guillain-Barré Syndrome after receiving flu vaccination
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Many pharmaceutical companies rush to manufacture vaccines for possible flu pandemics. The problem with these vaccines is that they are produced by non-egg-based techniques which provide rapid synthesis at relatively cheaper cost. There have been more than 70 clinical trials to evaluate these vaccines and some have been completed. But the real cost effectiveness and safety is yet to be determined<sup>11</sup>.

## Management

The usual treatment of influenza is to take a rest, drink plenty of fluids, take paracetamol for the body aches and fever, antihistamines to reduce the congestion and avoid smoking. Antibiotics are frequently used to prevent or to treat secondary bacterial infections.

Antiviral drugs have been introduced after 2009 pandemic. There are two classes of antiviral drugs, neuraminidase inhibitors such as oseltamivir (Tamiflu) and zanamivir (Relenza) and M2 inhibitors such as amantadine and rimantadine, see table 4.

**Table 4: Classes of Antiviral Drugs<sup>6</sup>**

Neuraminidase Inhibitors	M2 Inhibitors
<ul style="list-style-type: none"> <li>• May be effective against both influenza A and B</li> </ul>	<ul style="list-style-type: none"> <li>• These drugs are sometimes effective against influenza A if given early in the infection but are always ineffective against influenza B</li> </ul>
<ul style="list-style-type: none"> <li>• Scientific reliability is low</li> </ul>	<ul style="list-style-type: none"> <li>• Measured resistance to amantadine and rimantadine in American isolates of H3N2 has increased to 91% in 2005</li> </ul>
<ul style="list-style-type: none"> <li>• Different strains of influenza viruses have differing degrees of resistance against these antivirals</li> </ul>	<ul style="list-style-type: none"> <li>• The CDC recommended against using M2 inhibitors during the 2005/06 influenza season due to high levels of drug resistance</li> </ul>
<ul style="list-style-type: none"> <li>• It is impossible to predict what degree of resistance a future pandemic strain might have</li> </ul>	
<ul style="list-style-type: none"> <li>• The FDA deems their effect to be modest</li> </ul>	

The dosages are further explained in table 5. In general it is recommended to administer both antibacterial and antiviral drugs if there are signs of pneumonia<sup>13</sup>. Based on the medical history of the patient, his current symptoms and the evidence based clinical recommendations, the physician can choose the management plan for a patient presenting with influenza. Whether to administer antiviral drugs during the flu season or not is a matter of weighing the pros and cons plus bearing in mind the stage of the illness and risk factors.

**Table 5: Recommended Dosage and Schedule of Influenza Antiviral Medications\* for Treatment\*\* and Chemoprophylaxis\*\*\* (13)**

Antiviral Agent		Age Group (yrs)				
		1 - 6	7 - 9	10 - 12	13 - 64	≥ 65
Zanamivir	Treatment, influenza A and B	NA	10 mg (2 inhalations) twice daily			
	Chemoprophylaxis, influenza A and B	NA for ages 1 - 4	(Ages 5 and above) 10 mg (2 inhalations) once daily			
Oseltamivir <sup>¶</sup>	Treatment,**** influenza A and B	Dose varies by child's weight***** (>40 kg = adult dose)			75 mg twice daily	
	Chemoprophylaxis, influenza A and B	Dose varies by child's weight***** (>40 kg = adult dose)			75 mg once daily	

**Abbreviation:** NA = not approved

\*Zanamivir is manufactured by GlaxoSmithKline (Relenza - inhaled powder). Zanamivir is approved for treatment of persons aged  $\times 7$  years and approved for chemoprophylaxis of persons aged  $\times 5$  years. Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease. Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu -- tablet). Oseltamivir is approved for treatment or chemoprophylaxis of persons aged  $\times 1$  year. Oseltamivir is available for oral administration in 30 mg, 45 mg and 75 mg capsules and liquid suspension. No antiviral medications are approved for treatment or chemoprophylaxis of influenza among children aged  $< 1$  year. This information is based on data published by the Food and Drug Administration (FDA).

\*\*Recommended duration for antiviral treatment is 5 days. Longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.

\*\*\* Recommended duration is 10 days when administered after a household exposure and 7 days after the most recent known exposure in other situations. For control of outbreaks in long-term care facilities and hospitals, CDC recommends antiviral chemoprophylaxis for a minimum of 2 weeks and up to 1 week after the most recent known case was identified.

¶ See Table 4 for information about use of oseltamivir for infants aged  $< 1$  year. A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance  $< 30$  mL/min.

\*\*\*\* The treatment dosing recommendation for oseltamivir for children aged  $\times 1$  year who weigh  $\leq 15$  kg is 30 mg twice a day. For children who weigh  $> 15$  kg and up to 23 kg, the dose is 45 mg twice a day. For children who weigh  $> 23$  kg and up to 40 kg, the dose is 60 mg twice a day. For children who weigh  $> 40$  kg, the dose is 75 mg twice a day.

\*\*\*\*\* The chemoprophylaxis dosing recommendation for oseltamivir for children aged  $\times 1$  year who weigh  $\leq 15$  kg is 30 mg once a day. For children who weigh  $> 15$  kg and up to 23 kg, the dose is 45 mg once a day. For children who weigh  $> 23$  kg and up to 40 kg, the dose is 60 mg once a day. For children who weigh  $> 40$  kg, the dose is 75 mg once a day.

**Potential conflicts of interest:** No

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